AMENDMENT

In the Claims:

Please amend claims 1, 32 and 43, so that the text of the amended claims reads as follows:

1. (Amended) A kit comprising, in a pharmaceutically acceptable form, biologically effective amounts of at least a first anti-cancer agent, wherein said at least a first anti-cancer agent is at least a first targeting agent-therapeutic agent construct that comprises at least a first targeting agent that binds to an aminophospholipid operatively attached to at least a first therapeutic agent; and:

(a) a targeting agent-detectable agent construct that comprises a second targeting agent that binds to an aminophospholipid operatively attached to a detectable agent; or

(b) at least a second anti-cancer agent other than said at least a first targeting agent-therapeutic agent construct.

32. (Amended) The kit of claim 1, wherein said kit comprises biologically effective amounts of:

(a) said at least a first targeting agent-therapeutic agent construct that comprises at least a first targeting agent that binds to an aminophospholipid operatively attached to at least a first therapeutic agent;

(b) said targeting agent-detectable agent construct that comprises a second targeting agent that binds to an aminophospholipid operatively attached to a detectable agent; and

(c) said at least a second anti-cancer agent.

43. (Twice Amended) In combination, biologically effective amounts of:

(a) a first composition comprising at least a first anti-cancer agent, wherein said at least a first anti-cancer agent is at least a first targeting agent-therapeutic agent construct that comprises at least a first targeting agent that binds to an aminophospholipid operatively attached to at least a first therapeutic agent;

(b) a second composition comprising a targeting agent-detectable agent construct that comprises a second targeting agent that binds to an aminophospholipid operatively attached to a detectable agent; and

(c) at least a second anti-cancer agent other than said at least a first targeting agent-therapeutic agent construct.

Please add claim 50 as follows:

50. (New) The kit of claim 1, wherein said kit comprises at least a first pharmaceutically acceptable liposomal formulation.

RESPONSE

I. Status of the Claims

Prior to the present Action, claims 1-32 and 43-49 were pending. The Action at the Summary page and at page 2, Item 1, is believed to be in error in listing claims 1-30 and 43-49 as pending (see **Section III** for discussion of restriction). Indeed, claim 32 is said to be free of the art (Action at page 10, Item 30). According to a species election requirement, claims 10-15, 20-23 and 44 are said to be withdrawn as reading on the non-elected species, although these claims have been examined (see **Section III** for discussion of species).

Presently, no claims have been canceled. Claims 1, 32 and 43 have been amended to even further improve their clarity. Claim 50 has been added, which is fully supported by the application as filed and unified with the examined claims.

Claims 1-32 and 43-50 are therefore in the case. According to 37 C.F.R. § 1.121, and for the convenience of the Examiner, a clean copy of the pending claims is included (**Exhibit A**), along with a copy of the claims showing the present revisions (**Exhibit B**). The claims in each are marked "(Amended)" or "(New)", where appropriate.

II. Support for the Claims

Support for the amended claims and the new claim is to be found throughout the original application as filed. Any small entity fees necessary for the introduction of the new claim should be deducted from Williams, Morgan & Amerson, P.C. Deposit Account No. 50-0786/ 3999.002383.

Claim 1 has been revised to even further clarify that the at least a first targeting agent-therapeutic agent construct of the claimed kits is "at least a first anti-cancer agent". This is supported throughout the specification, *e.g.*, at least at page 39, lines 3-5. The at least a second anti-cancer agent in claim 1 has also been defined as a second anti-cancer agent "other than" the targeting agent-therapeutic agent construct that forms the first anti-cancer agent. This is also supported by the foregoing text in the specification at page 39, with additional support in Section G, where the specification states "each of the therapeutic agent-targeting agent construct and other anti-cancer agent components of the kit" (specification at page 137, lines 26-28, emphasis added).

Claim 32 has been revised to use the term "said" to better relate each of elements (a), (b) and (c) to claim 1.

In claim 43, elements (a) and (c), the changes are the same as those described above for elements (a) and (b) of claim 1, and are similarly supported in the specification.

Finally, claim 50 is a new dependent claim directed to liposomal formulations. This is supported by original claims 1 and 19 and at various points of the specification, particularly in Section F2, directed to liposomes and nanoparticles (specification at pages 136-137).

It will therefore be understood that no new matter is included within the amended or new claims.

III. Restriction and Species Issues

The Action at the Summary page and at page 2, Item 1, lists the claims pending prior to the present response as claims 1-30 and 43-49. An accurate listing of the claims is claims 1-32 and 43-49, which represent the Group I invention set forth in the Second Restriction Requirement, dated May 09, 2000. Subsequent sections of the present Action also include claims 30-32 within the examined claims, and claim 32 is said to be free of the art (Action at page 10, Item 30).

The Action at page 2, Items 2 and 3, states that claims 10-15, 20-23 and 44 are withdrawn from "further" consideration, as being drawn to a nonelected species, and that these claims must be canceled in reply to a final rejection. These sections of the Action also state that the species elections were made "with traverse", variously in papers No. 14 and 15. Each of these aspects of the Action is in error.

First, claims drawn to nonelected species are not withdrawn from "further" consideration, but remain pending and are rejoined upon allowance of a generic or other linking claim. 37 C.F.R. § 1.141(a). As pointed out in Applicants' earlier response, many of the claims drawn to the originally non-elected species have, in fact, already received an examination on the merits.

Second, the species elections were made without traverse in the response to the Second Restriction Requirement (see Applicants' response dated August 03, 2000, Section V, last paragraph, first sentence).

IV. Inventorship

The Office appears to indicate an intent to grant Applicants' petition to correct inventorship under 37 C.F.R. § 1.48(a). However, it is alleged that the materials submitted did not contain a new Inventors' Oath or Declaration executed by the actual inventors (Action at page 2, Item 4).

In contrast, Applicants' records show the presence of a new Inventors' Declaration executed by each of the actual inventors, Philip E. Thorpe, Sophia Ran and Rolf A. Brekken (copy enclosed). This is listed as Item 5 on the covering letter and itemized on the postcard, which was returned by the Office to evidence receipt.

Nonetheless, Applicants have obtained another Inventors' Declaration executed by each of Philip E. Thorpe, Sophia Ran and Rolf A. Brekken and enclose the original document. This completes the requirements for changing inventorship and Applicants respectfully request that the change be recorded.

V. Rejection of Claims 1-9, 16-19, 24-32, 43 and 45-48 Under 35 U.S.C. § 112, Second Paragraph

The Action first rejects claims 1-9, 16-19, 24-32, 43 and 45-48 under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite and for failing to particularly point out and distinctly claim the subject matter of the invention. Although Applicants respectfully traverse, the Action's concerns are fully addressed.

Claim 49 is free from this ground of rejection.

The Action alleges that the recitation of "at least a second anti-cancer agent" in the claims is ambiguous (Action at Item 7).

The Action continues to characterize Applicants' position as being that the "'first' anti-cancer agent is 'the first antibody, or an antigen binding fragment thereof, that binds to an aminophospholipid'" and that the specification includes detailed teaching "concerning the use of naked anti-aminophospholipid antibody as the first anti-cancer agent" (Action at Item 8). The Action further states that "the instant claims are not directed to 'naked anti-aminophospholipid antibodies', nor are they reciting the term 'the first anti-cancer agents' as described in the specification at page 32, lines 1-9" (Action at Item 9). At Item 10, the Action continues to criticize the specification at page 32, lines 1-9.

Applicants are perplexed at the foregoing sections of the Action, which constitute the entire reasoning in support of the second paragraph rejection. The present invention is not concerned with naked anti-aminophospholipid antibodies, but is directed to kits comprising a therapeutic agent-targeting agent construct in which the targeting agent binds to an aminophospholipid. Applicants have also studied page 32 and cannot discern the relevance of the cited text.

It appears that the Office has been considering Application Serial No. 09/351,862 by Philip E. Thorpe and Sophia Ran ("the '862 application"; Attorney Docket Nos. 4001.002282 and UTSD:549--1), although Applicants are troubled by this possibility and the implications thereof. Nonetheless, even as applied to the present application, the rejection is improperly founded and overcome.

As explained in the specification at page 39, in those aspects of the claimed invention where the kits comprise an anti-cancer agent "in addition to the therapeutic agent-targeting agent

construct of the invention", it does not matter whether the therapeutic agent-targeting agent construct or the additional anti-cancer agent is termed the first or second anti-cancer agent.

Claims 1, 32 and 43 have been revised to unambiguously state that the "at least a first anti-cancer agent" is the first targeting agent-therapeutic agent construct, and that the at least a second anti-cancer agent is an anti-cancer agent "other than" the first targeting agent-therapeutic agent construct. These clarifications directly address the Action's concern at Item 10.

The rejection under 35 U.S.C. § 112, second paragraph is therefore overcome and should be withdrawn.

VI. Rejection of Claims 1, 3-5 and 8 Under 35 U.S.C. § 102(b)

The Action next rejects claims 1, 3-5 and 8 under 35 U.S.C. § 102(b) as allegedly being anticipated by Fishman *et al.*, *Intl. J. Oncol.*, 10:901-904, 1997 ("Fishman"). Although Applicants respectfully traverse, the Action's concerns are addressed.

A rejection on the grounds of anticipation requires the disclosure, in a single reference, of every element of a claimed invention and requires that each and every facet of the claimed invention be identified in the applied reference. *Ex parte Levy*, 17 USPQ2d 1461 (B.P.A.I. 1990); *Minnesota Mining & Mfg. v. Johnson & Johnson Orthopaedics, Inc.*, 24 USPQ2d 1321 (Fed. Cir. 1992).

Fishman is cited as disclosing "anti-phospholipid antibodies directed to melanoma cells and other the [*sic*] cancer cells having over expressed outer membrane phosphatidylserine" and as "purifying IgG anti-PS antibodies from patients with antiphospholipid syndrome and examining their *in vivo* efficacy against melanoma tumor cells ELISA tests" (Action at Item 13, page 5). Fishman more properly concerns various observations on autoimmunity and cancer.

The Action continues to allege that, as apparently argued in Applicants' response of September 28, 2001[1], and in view of the definition of the first and second anti-cancer agents at page 32 of the specification, "it appears that the second anti-cancer agent can be the same as the first anti-cancer agent" (Action at Item 14).

The continued reference to the specification at page 32, lines 1-9, and the assessment of the claimed invention as encompassing "anti-aminophospholipid antibodies" (Action at Item 14), appear to be an ongoing reference to the foregoing '862 application and are not relevant to the present application.

In any event, Applicants respectfully disagree with the assessment of Applicants' last response and the specification at page 39 as teaching that the second anti-cancer agent can be the same as the first anti-cancer agent (Action at Item 14). The instant specification at page 39, for example, explains that it is irrelevant as to which of the two anti-cancer agents of the claimed kits is termed "first" or "second", simply for grammatical purposes. Therefore, should a different interpretation be maintained, Applicants respectfully requested that the Office expand on the reasoning for the different interpretation in light of the present response.

The Action next states "it is Examiner's position that Fishman's separate doses of anti-PS antibodies meets the limitations of the instant claims because they are directed to two separate anti-cancer agents" (Action at Item 14, page 6). This statement contains a number of errors. First, as indicated above, the presently claimed invention is not directed to anti-PS antibodies, whether in separate doses or in combination with anti-cancer agents, but is directed to kits comprising aminophospholipid targeting agent-therapeutic agent constructs.

[1] The response was filed September 13, 2001, and received in the Office on September 24, 2001. Applicants believe the reference to September 28, 2001 again concerns Application Serial No. 09/351,862.

Second, Applicants have studied Fishman and can find no mention of "separate doses of anti-PS antibodies", as alleged in the Action, or separate doses of any targeting agent construct involving an anti-PS antibody. Should the Office continue with this line of reasoning, Applicants therefore respectfully request that the particular portion of Fishman believed to teach separate doses of anti-PS antibodies be identified.

Third, and importantly, should the Office intend to take the position that Fishman is "directed to two separate anti-cancer agents", Applicants respectfully request that the particular portion of Fishman relied upon be pointed out.

Finally under this section, the Action assesses Fishman as teaching "the potential use of autoantibodies in diagnostic and therapeutic area [*sic*] such as treatment of squamous cell carcinoma of the skin" (Action at Item 14). Applicants again stress that the claimed invention is not directed to antibodies, whether autoantibodies or not. More importantly, the references in Fishman to squamous cell carcinoma treatment are totally separate from anti-PS antibodies, and rather concern anti-keratinocyte antibodies (Fishman at Table I, last line; page 903, second column, paragraph beginning "b)").

In summary, the present specification and claims make it clear that the kits of the invention contain two distinct anti-cancer agents, one of which is a targeting agent-therapeutic agent construct that binds to an aminophospholipid. Fishman does not teach the combination of such a targeting agent-therapeutic agent construct with a second anti-cancer agent. Fishman also fails to teach or suggest a targeting agent-therapeutic agent construct that binds to an aminophospholipid in conjunction with a detectably labeled antibody that also binds to an aminophospholipid. Fishman thus clearly fails to anticipate the claimed invention. *Minnesota Mining & Mfg., supra.*

The rejection under 35 U.S.C. § 102(b) over Fishman is therefore overcome and should be withdrawn.

VII. Rejection of Claims 1, 2-9 and 14 Under 35 U.S.C. § 102(e)

The Action next rejects claims 1, 2-9 and 14 under 35 U.S.C. § 102(e) as allegedly being anticipated by U.S. Patent No. 6,300,308 to Schroit ("Schroit"). Although Applicants respectfully traverse, the Action's concerns are addressed.

The Action at Item 15 rejects claims 1, 2-9 and 14 over Schroit, which is first cited as disclosing "methods for inhibiting cancer cell growth or killing cancer cells comprising eliciting a lipid specific antibody response with an immunologically effective amount of composition comprising a phophatidylserine/polypeptide [*sic*] conjugate" (Action at page 6).

As the presently claimed invention is not drawn to methods, but to kits comprising a therapeutic agent-targeting agent construct in which the targeting agent binds to an aminophospholipid and either a detectably-labeled aminophospholipid targeting agent or a second anti-cancer agent, the methods of Schroit are not relevant to a rejection under § 102(e). The phosphatidylserine-polypeptide conjugates for use in the Schroit methods are not pertinent to the rejection, as the claimed components of the present kits are not phosphatidylserine-polypeptide conjugates.

The Action at page 6 continues to describe Schroit as disclosing "kits comprising a lipid or lipid-carrier conjugate antigen-specific antibodies with suitable immunodetecting reagents such as detectable labels linked to a protein, peptide or antibody directed to aminophospholipid receptors in suitable pharmaceutical formulations", and cites Schroit at column 6, lines 65-68, column 7, lines 13-35, "example" and column 23, lines 29-65. The Action's reference to an

antibody directed to "aminophospholipid receptors" is not understood, and Applicants respectfully request clarification of this terminology and the intended meaning.

Schroit at column 6, line 65 to column 7, line 3 and at column 7, lines 13-35 (in part) concerns immunodetection kits and methods using immunodetection reagents alone. Although the immunodetection can be achieved using a first, labeled antibody (column 6) or a second labeled antibody (column 7, lines 1-3)[2], there is no reference to any therapeutic agent in the Schroit kits at columns 6 and 7. Schroit at columns 6 and 7 also lacks any reference to "pharmaceutical formulations", and the Action is therefore in error in this assessment of Schroit.

In contrast to the immunodetection kits of Schroit, the detectably-labeled anti-aminophospholipid antibodies encompassed within the kits of the present invention are always present in combination with a therapeutic conjugate, *i.e.*, the aminophospholipid targeting agent-therapeutic agent construct recited in the kits. Thus, the section of Schroit from column 6, line 65 to column 7, line 3 is not relevant to an anticipation rejection as it lacks a key feature of the claimed invention, namely the therapeutic conjugate. *Minnesota Mining & Mfg., supra.*

The next quoted section of Schroit, column 23, lines 29-65, concerns the preparation of PS-carrier conjugates and the production of antisera from rabbits immunized against PS-BSA. This section of Schroit is not germane to the claimed invention, *i.e.*, to kits containing an aminophospholipid targeting agent-therapeutic agent construct in combination with a second anti-cancer agent or a detectably-labeled anti-aminophospholipid antibody, and does not support the § 102(e) rejection.

[2] Although column 7 mentions in passing that antibodies can be used in detection, the emphasis of column 7 concerns the use of a lipid and/or lipid conjugate in detection, which is not relevant to the claimed invention.

The Action next states, "Schroit sets forth that his PS-specific antibodies can be used in for [*sic*] prevention and treatment of conditions such as cancer wherein surfaces of the cells causing the condition are characterized by the presence of PS on their external leaflet" and cites Schroit at column 16, lines 38-44 and column 19, lines 36-67 (Action at page 6, third sentence).

Applicants have studied Schroit at column 16, lines 38-44 and column 19, lines 36-67 and cannot find a disclosure that teaches or suggests a kit comprising any form of anti-aminophospholipid antibody, whether naked or conjugated, in combination with a second anti-cancer agent or a detectably-labeled anti-aminophospholipid antibody. The Action's focus on Schroit's "PS-specific antibodies" is particularly irrelevant as the kits of the present invention are not directed to combinations of "PS-specific antibodies", but to combinations of aminophospholipid targeting agent-therapeutic agent constructs.

The § 102(e) rejection at Item 15 is therefore overcome and should be withdrawn.

The Action continues with the § 102(e) rejection over Schroit at Item 16, stating "Schroit also discloses therapeutic kits comprising one or more lipid conjugate antigens or antibodies directed to phosphatidylserine receptors[3] in separate containers" (col 7, lines 40-67; col 8, lines 1-40; col 28, lines 1-67); subsequently, the kits of Schroit contain at least two anticancer agents" (Action at Item 16, bridging pages 6 and 7; emphasis added).

The Action has again overlooked the important fact that the kits of the present invention do not recite "PS-specific antibodies" as part of the claimed combinations, but are directed to "aminophospholipid targeting agent-therapeutic agent constructs" in combination with aminophospholipid targeting agent-detectable agent constructs or second, distinct anti-cancer agents.

[3] The reference to antibodies directed to "phosphatidylserine receptors" is not understood, and Applicants again respectfully request clarification from the Office.

In any event, the Action's assessment of Schroit, even as pertaining to "PS-specific antibodies", and the resultant § 102(e) rejection, are in error. To the extent that Schroit concerns kits with "distinct container means" (Schroit at column 7, line 66), Schroit states:

> "In such cases, one or more containers would contain each of the PS composition(s), either as sterile solutions, powders, lyophilized forms, etc., and the other container(s) would include a matrix, solution, or other suitable delivery device for applying the composition to the body, bloodstream, or to a tissue site, skin lesion, tumor cell, wound area, or other site of administration. Such delivery device may or may not itself contain a sterile solution, diluent, gelatinous matrix, carrier or other pharmaceutically-acceptable components. The kits may also comprise a second or third container means for containing a sterile, pharmaceutically acceptable buffer, diluent or solvent".
>
> Schroit at column 7, line 66 to column 8, line 11; emphases added.

Thus, the Action wrongly concludes that Schroit discloses one or more lipid conjugate antigens or antibodies directed to phosphatidylserine receptors in separate containers. As shown above, the "other container(s)" of Schroit include either a delivery device for application to the body or a pharmaceutically acceptable buffer. The quoted section at column 28, lines 1-67 does not support the Action's position, as this simply describes the generation of phosphatidylserine/ phosphatidylcholine β2-glycoprotein I conjugates and the immunization of mice prior to inoculation with tumor cells. Combination kits are not disclosed at column 28.

Even assuming, *arguendo*, that Schroit at columns 7, 8 and/or 28 disclosed one or more antibodies directed to phosphatidylserine in separate containers, as suggested in the Action, this does support the Action's conclusion that Schroit anticipates the claimed invention. The requirement for an aminophospholipid targeting agent-therapeutic agent construct has again been overlooked. The therapeutic kits of the claimed invention are, anyway, not kits just containing one or more aminophospholipid targeting agent-therapeutic agent constructs in separate containers. Rather, the claimed kits contain at least a first aminophospholipid targeting agent-

therapeutic agent construct in combination with at least a second, distinct anti-cancer agent, *i.e.*, another anti-cancer agent other than the aminophospholipid targeting agent-therapeutic agent construct (specification at page 137, lines 26-28). Thus, even a liberal interpretation of Schroit at columns 7, 8 and/or 28 fails to support the rejection.

The Action next characterizes Schroit as teaching "combination of his antibodies with a secondary anti cancer agents [*sic*] such as diphtheria toxoid", and cites Schroit at column 8, lines 65-67 (Action at page 7). In addition to ignoring the need for an aminophospholipid targeting agent-therapeutic agent construct, Applicants respectfully point out that the Action has mischaracterized this section of Schroit.

Rather than teaching the use of diphtheria toxoid as an anti-cancer agent, Schroit at column 8, lines 58-67 teaches that with respect to preparing lipid-specific antibodies, "it is necessary to boost the host immune system", which may be achieved by coupling the lipid of interest to a carrier. Diphtheria toxoid is set forth as one example of such a carrier, along with KLH, BSA, β2-glycoprotein I, albumins such as ovalbumin, mouse serum albumin or rabbit serum albumin, and bovine gamma globulin (Schroit at column 8, lines 58-67). Thus, the diphtheria toxoid of Schroit is a carrier for lipid immunization, not a secondary anti-cancer agent, and Schroit is not anticipatory.

Moreover, diphtheria toxoid is not included within the scope of the present claims as a carrier for immunization, because the Schroit "carriers" are conjugated to the "lipid of interest". The present kits are not concerned with lipids for immunization, but with aminophospholipid targeting agent-therapeutic agent constructs for use as therapeutics, in combination with other anti-cancer agents or aminophospholipid diagnostic constructs.

Finally, whether or not Schroit discloses the use of humanized or recombinant antibodies in preparing his compositions (Action at page 7) is not relevant to the present enquiry. As Schroit does not teach or suggest a kit comprising an aminophospholipid targeting agent-therapeutic agent construct and either a detectably-labeled aminophospholipid targeting agent or a second anti-cancer agent other than the aminophospholipid targeting agent-therapeutic agent construct, Schroit fails to anticipate the claimed invention irrespective of any discussion of humanized or recombinant antibodies.

Applicants' foregoing response to the reasoning set forth in Action should not be interpreted as acquiescing that the effective filing of date Schroit is earlier than the effective filing date of the present invention. Nor should this be interpreted as Applicants waiving any rights to establish a date of invention earlier than the effective filing date of Schroit.

For at least the above reasons, Schroit is not competent prior art and fails to anticipate the claimed invention. The rejection under 35 U.S.C. § 102(e) over Schroit is thus overcome and should be withdrawn.

VIII. Rejection of Claims 1-9, 16-19, 24-31, 43 and 45-49 Under 35 U.S.C. § 103(a)

The Action next rejects claims 1-9, 16-19, 24-31, 43 and 45-49 under 35 U.S.C. § 103(a) as allegedly being legally obvious over the foregoing Schroit patent in view of U.S. Patent No. 5,632,991 to Gimbrone ("Gimbrone"); U.S. Patent No. 6,197,278 to Blankenberg *et al.* ("Blankenberg") and Umeda *et al.*, *J. Immunol.*, 143:2273-2279, 1989, ("Umeda"). Although Applicants respectfully traverse, the Action's concerns are fully addressed.

Before addressing the rejection as seems to have been intended, Applicants respectfully point out that the rejection is *prima facie* improper and Applicants are not, in fact, required to respond. The rejection as stated in the Action at Item 18, page 8, relies on Umeda as the fourth

reference in the cited combination. The text of the Action that follows, however, does not discuss Umeda, and thus fails to establish either a proper combination or a *prima facie* rejection. Applicants respond as a courtesy and to progress the application to allowance as soon as possible.

For an obviousness rejection to be proper under 35 U.S.C. § 103(a), it is required that the cited prior art suggest to those of ordinary skill in the art that they should make the claimed composition or device, or carry out the claimed process; and that the prior art also convey to those of ordinary skill a reasonable expectation of success. *In re Dow Chemical Co.*, 5 USPQ 2d 1529, 1531 (Fed. Cir. 1988). Both the suggestion and the reasonable expectation of success must be founded in the prior art, not in the applicant's disclosure. *Id.*

When, as in the present case, an obviousness rejection depends on a combination of prior art references, there must be some teaching, suggestion or motivation to combine the references. *In re Rouffet*, 47 USPQ2d 1453, 1456 (Fed. Cir. 1998). Even if every element of an invention can be found in the prior art, obviousness is not established in the absence of sufficient "motivation to combine". *Rouffet* at 1457-1458. A high level of skill in the art cannot be held to substitute for the required motivation to combine. *Rouffet* at 1458.

Properly combined references, even if providing some suggestion towards the invention, are insufficient to establish legal obviousness unless they also provide "a reasonable expectation of success". *In re Dow Chemical Co., supra; In re Vaeck*, 20 USPQ2d 1438, 1442 (Fed. Cir. 1991). Both the suggestion and the reasonable expectation of success must be founded in the prior art, not in the applicant's disclosure. *Id.*

The Action states that Schroit "fails to specifically disclose the use of other suitable antiphospholipid antibodies in combination with an anti-cancer agent conjugated to a targeting

antibody" (Action at Item 18, page 8). The requirement for an aminophospholipid targeting agent-therapeutic agent construct, rather than an antibody, in the presently claimed invention has again been ignored.

As detailed above (**Section VII**), Schroit in fact fails to teach or suggest the use of a kit comprising a naked anti-aminophospholipid antibody, or an aminophospholipid targeting agent-therapeutic agent construct, in combination with any anti-cancer agent. Schroit therefore fails to teach or suggest any kits of relevance to the present invention. The admitted failure to disclose additional anti-cancer agents in the form of antibody-therapeutic agent constructs is just one particular omission in Schroit.

Gimbrone is first cited as disclosing "targeting agents conjugated to an antibody directed to ELAM-1 (E-selectin)" (Action at Item 19, page 8). Applicants are perplexed regarding the Action's use of the term "targeting agents conjugated to an antibody", and respectfully request that the Office explain the intended meaning. The Action next states, "Gimbrone teaches that such endothelial specific adhesion molecules are rapidly unregulated on the surface of cultured human vascular endothelial cells (Action at page 8; emphasis added). Applicants cannot discern the relevance of the stated presence of unregulated endothelial specific adhesion molecules on cultured human vascular endothelial cells to the present invention, and appropriate clarification is respectfully requested.

The Action at page 8, further states, "Gimbrone also discloses the use of his targeting agent-therapeutic agent conjugate, alone or in combination with other antibody or antibody fragment and/or a therapeutic agent (a second anti-cancer agent)" and cites Gimbrone at column 15, lines 46-55 (Action at page 8). As pointed out in Applicants' first response, even if this assessment of Gimbrone was accurate, the present invention is not directed to E-selectin

targeting agent-therapeutic agent conjugates, but to kits comprising an aminophospholipid targeting agent-therapeutic agent construct in combination with either a detectably-labeled aminophospholipid targeting agent or a second anti-cancer agent.

In any event, the Action's assessment of Gimbrone is in error. Gimbrone at column 15, lines 46-55 does not disclose an E-selectin targeting agent-therapeutic agent conjugate "in combination with other antibody or antibody fragment and/or a therapeutic agent (a second anti-cancer agent)". Rather, this section of Gimbrone is entirely limited to the use of an "E-selectin specific monoclonal antibody, or antibody fragment" (Gimbrone at column 15, lines 43-44) or an "E-selectin specific monoclonal antibody [is] conjugated to an anti-inflammatory agent, anti-thrombotic agent, anti-complement agent, or immunosuppressive agent" (Gimbrone at column 15, lines 49-52), each of which are used alone, not in combination.

Gimbrone at column 15, lines 46-55 therefore does not mention a kit comprising an E-selectin antibody or antibody conjugate in combination with any second therapeutic agent, let alone a second anti-cancer agent. Gimbrone particularly lacks any teaching or suggestion of a kit comprising an anti-E-selectin antibody conjugate in combination with an anti-aminophospholipid antibody (as later acknowledged in the Action at page 8) or with an aminophospholipid targeting agent-therapeutic agent construct.

The Action next takes the position that the "therapeutic agents of Gimbrone produce apoptosis as they encompass various toxins, antioxidants and anti-tumor drugs", citing Gimbrone at columns 12-14 and claim 2 (Action at page 8). As cleared recited in claims 1 and 2 of Gimbrone, this teaching is entirely confined to immunoconjugates comprising the anti-E-selectin antibody, H18/7, conjugated to a therapeutic agent. Equally, Gimbrone at columns 12-14 is limited to the use of anti-E-selectin antibodies alone or anti-E-selectin antibody conjugates alone.

Gimbrone at columns 12-14 does not suggest an anti-E-selectin antibody conjugate in combination with any distinct toxin, antioxidant or anti-tumor drug, and is far removed from suggesting combination with an anti-aminophospholipid antibody (as later acknowledged in the Action at page 8) or with an aminophospholipid targeting agent-therapeutic agent construct.

Gimbrone at column 13, lines 58-67 is further said to teach that E-selectin or a leukocyte binding fragment thereof can be coupled to a chemotherapeutic drug that binds to tumor cells expressing receptors for E-selectin, to kill the tumor cells (Action at page 8). Again, this reference is limited to the use of a single therapeutic conjugate, and does not include any suggestion of combinations with second anti-cancer agents, particularly not combinations with an anti-aminophospholipid antibody (as later acknowledged in the Action at page 8) or with an aminophospholipid targeting agent-therapeutic agent construct.

Thus, Gimbrone is entirely limited to suggestions for using various single therapeutic agents based upon E-selectin or anti-E-selectin antibodies or conjugates thereof. Gimbrone does not teach or suggest any combination therapies with anti-aminophospholipid antibodies (as agreed in the Action at page 8), or with an aminophospholipid targeting agent-therapeutic agent construct. Schroit concerns lipid-carrier protein conjugate compositions for generating lipid-specific immune responses in an animal (Schroit at abstract). Schroit does not concern E-selectin or anti-E-selectin antibodies or conjugates, and does not teach or suggest any combination therapies with E-selectin-based therapeutics.

Before the P.T.O. may combine the disclosure of two or more prior art references in order to establish *prima facie* obviousness, there must be some suggestion for doing so, found either in the references themselves or in the knowledge generally available to one of skill in the art. *In re Fine*, 5 USPQ2d 1596, 1598-99 (Fed. Cir. 1988). As Gimbrone does not concern lipid-carrier

protein conjugates, lipid-specific immune responses, aminophospholipids or anti-aminophospholipid antibodies, and Schroit does not concern E-selectin, anti-E-selectin antibodies, antibody conjugates or therapeutic methods based upon E-selectin, the references have been improperly combined.

As to diagnostic kits, the Action characterizes Gimbrone as disclosing methods for detecting E-selectin expression within the body of a patient comprising steps of detecting E-selectin by labeling the E-selectin antibody with a radioactive isotope that can be detected, citing Gimbrone at column 18, lines 60-65 (Action at page 9).

This is particularly far removed from the present invention, as the diagnostic embodiments within the claimed kits require a targeting agent-detectable agent construct that comprises a second targeting agent that binds to an aminophospholipid operatively attached to a detectable agent, in combination with the first targeting agent-therapeutic agent construct. Radioactively labeled anti-E-selectin antibodies have absolutely no relevance to the claimed invention.

As to the third reference in the combination, Blankenberg is cited as teaching targeted radiolabeled annexin V (Action at Item 20, page 9). As Blankenberg does not concern anti-aminophospholipid antibodies, this document has been cited against claims drawn to the non-elected species. Moreover, as Blankenberg does not concern anti-aminophospholipid antibodies, the Action is in error in the assessment of Schroit, Gimbrone, Umeda and Blankenberg as being directed to the field of antibody immunology (Action at Item 21). The references have thus been improperly combined.

The Action admits that Blankenberg does not teach the use of a therapeutic agent (Action at Item 20, page 9). Whilst Applicants agree with this deficiency, it is more important to note

that Blankenberg fails to teach or suggest the key component of the present invention: a targeting agent-therapeutic agent construct comprising a targeting agent that binds to an aminophospholipid operatively attached to at least a first therapeutic agent. As Blankenberg concerns only diagnostic constructs of annexins, and not therapeutic constructs, Blankenberg has no relevance to the claimed invention.

Applicants had earlier asked the Office to identify the sections of Blankenberg that were believed to concern therapeutic constructs or methods, but no such text has been identified in the latest Action. Neither does the latest Action respond to Applicants' earlier explanation of why Blankenberg teaches away from the claimed invention by concerning imaging apoptosis.

The Action does not discuss Umeda, which makes the rejection as a whole *prima facie* improper. Indeed, as the perceived relevance of Umeda to the present rejection cannot actually be assessed, Applicants cannot respond in any detail. Nonetheless, Applicants have studied Umeda and cannot identify a teaching or suggestion relevant to the presently claimed invention.

Applicants also respectfully point out that should Umeda later be used alone or in combination with other references as part of a rejection under 35 U.S.C. §§ 102 or 103, this would have to be made as part of a non-Final Office Action, being a new ground of rejection not necessitated by Applicants' amendment or late submission of references.

The Action further alleges that the teachings of Schroit, Gimbrone, Umeda and Blankenberg are in the same field of endeavor "as they are all directed to the field of antibody immunology" (Action at Item 21, page 9). As stated above, as Blankenberg does not in fact concern antibodies, the Action has both wrongly characterized the cited references as being directed to the field of antibody immunology and improperly combined the references.

Applicants further contest that Schroit, Gimbrone and Umeda are in the same field of endeavor, which position can only be reached by a significant extrapolation of each reference. More properly, Schroit concerns lipid-carrier protein conjugate compositions for generating lipid-specific immune responses, Gimbrone concerns E-selectin, anti-E-selectin antibodies and immunoconjugates and Umeda concerns stereo-specific recognition of phosphatidylserine by monoclonal antibody. In any event, even if Schroit, Gimbrone, Umeda and/or Blankenberg were all directed to the field of antibody immunology, the field of the present invention, as described in the opening sentence of the application, is the field of blood vessels and tumor biology.

Moreover, even if Schroit, Gimbrone, Umeda and Blankenberg are properly combined, these references in combination still fail to teach or suggest the kits of the claimed invention, drawn to an aminophospholipid targeting agent-therapeutic agent construct and either an aminophospholipid targeting agent- detectable agent construct or a second anti-cancer agent. The references in combination further fail to provide the reasonable expectation of success required to render the invention unpatentable.

The rejection under 35 U.S.C. § 103(a) is thus overcome and should be withdrawn.

IX. Double Patenting Rejection Over the '862 Application

Lastly, the Action provisionally rejects all examined claims under the judicially created doctrine of obviousness-type double patenting as allegedly being unpatentable over "pending claim" of the co-pending, '862 application (Action at page 10). Applicants respectfully traverse.

It is noted that the earlier double patenting rejection over application Serial No. 09/351,457 (now issued as U.S. Patent No. 6,312,694; Attorney Docket Nos. 3999.002300 and UTSD:556) has been withdrawn.

The Action states that the claims pending in this application are not patentably distinct from those in the '862 application "because they are both directed to kits comprising antibodies directed to aminophospholipids" (Action at Item 22, page 10). Applicants again respectfully point out that the claims in this application are not directed to kits comprising antibodies directed to aminophospholipids, but to kits comprising a targeting agent-therapeutic agent construct in which the targeting agent binds to an aminophospholipid. The rejection is therefore improperly founded.

MPEP 804 states that a double patenting rejection of the obviousness type is analogous to a failure to meet the nonobviousness requirement of 35 U.S.C. § 103, and such rejections therefore require application of the standards set forth in *Graham v. John Deere Co.*, 148 USPQ 459 (U.S.S.Ct. 1966). MPEP 804 at pages 800-22 to 800-24. The Action's discussion of the presently claimed invention and that of the '862 application does not meet the *Graham v. John Deere* standards for legal obviousness.

As the claims of the '862 application are directed to kits comprising naked or "unconjugated antibodies" and the claims of the present specification are directed to kits comprising "conjugated" therapeutic constructs, the Office is required to advance more detailed reasoning than presently offered in order to support the rejection.

In any event, a *provisional* rejection for obviousness-type double patenting between co-pending applications need not be addressed until the provisional double patenting rejection is the only rejection remaining in one or more of the applications. MPEP 804 at page 800-19, column 1. In such a circumstance, the rejection should be withdrawn in one of the applications, allowing the application to issue as a patent. MPEP 804 at page 800-19, column 2. When such a situation has been reached in the present and '862 applications, Applicants will then be in a

position to consider the propriety of any remaining rejection and the option of providing a Terminal Disclaimer. The case law is clear that the filing of a Terminal Disclaimer to obviate a rejection based on non-statutory double patent is not an admission of the propriety of the rejection. *Quad Environmental Technologies Corp. vs. Union Sanitary District*, 20 USPQ2d 1392 (Fed. Cir. 1991).

X. Conclusion

This is a complete response to the referenced Official Action. In conclusion, Applicants submit that, in light of the foregoing remarks and enclosed documents, the present case is in condition for allowance and such favorable action is respectfully requested. Should Examiner Sharareh have any questions or comments, or identify any informalities, a telephone call to the undersigned Applicants' representative is earnestly solicited.

Respectfully submitted,

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